PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MILES,JOHN S.
ERIC POTTER CLARKSON
Park View House
58 The Ropewalk
Nottingham NG1 5DD
GRANDE BRETAGNE

SS

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	09.10.2001
Applicant's or agent's file reference: KENF/P23194PC	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03660	25/09/2000	24/09/1999

International Patent Classification (IPC) or both national classification and IPC

A61K39/00

Applicant

THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF ...

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24/01/2002.

Name and mailing address of the international preliminary examining authority:
European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer / Examiner
Muller-Thomalla, K

Formalities officer (incl. extension of time limits)
Cardenas, C
Telephone No. +31 70 340 2370

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-79 as originally filed

Claims, No.:

1-55 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-10,13-15,23-25,49,50 and part of claims 26-48,

because:

   ☒ the said international application, or the said claims Nos. 1-4,6-10,13-15,23-25,49,50 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. Part of claims 1-3,6 and 26-50 and whole of claim 5.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	26,47,51-55
Inventive step (IS)	Claims	1-4,6-25,27-46,48-50
Industrial applicability (IA)	Claims	1-4,6-10,13-15,23-25,49,50

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The following documents were cited in the International Search Report:

D1: FOXWELL BRIAN ET AL: "Efficient adenoviral infection with IkappaBalpha reveals that macrophage tumor necrosis factor alpha production in rheumatoid arthritis is NF-kappaB dependent." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 14, 7 July 1998 (1998-07-07), pages 8211-8215, July 7, 1998 ISSN: 0027-8424

D2: EIGLER A ET AL: "Taming TNF: strategies to restrain this proinflammatory cytokine" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 18, no. 10, 1 October 1997 (1997-10-01), pages 487-492, ISSN: 0167-5699

D3: SEBBAG M ET AL: "Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-alpha, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 MAR) 27 (3) 624-32. ,

D4: WARD S G ET AL: "PI 3-kinase: a pivotal pathway in T-cell activation?" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 17, no. 4, 1 April 1996 (1996-04-01), pages 187-197, ISSN: 0167-5699

D5: BHATTACHARYYA S P ET AL: "Activated T lymphocytes induce degranulation and cytokine production by human mast cells following cell-to-cell contact." JOURNAL OF LEUKOCYTE BIOLOGY, (1998 MAR) 63 (3) 337-41. ,

D6: CHABOT S ET AL: "Microglial production of TNF - alpha is induced by activated T lymphocytes. Involvement of VLA-4 and inhibition by interferonbeta-1b." JOURNAL OF CLINICAL INVESTIGATION, (1997 AUG 1) 100 (3) 604-12.

D7 AVICE M N ET AL: "Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates TNF - alpha and IL-12 production by monocytes and dendritic cells." JOURNAL OF IMMUNOLOGY, (1999 MAR 1) 162 (5) 2748-53.

D8: US 5 085 985 A (MAINO VERNON C ET AL) 4 February 1992 (1992-02-04)

D9: MACLEAN J A ET AL: "Anti -CD3: anti - IL - 2 receptor bispecific monoclonal antibody. Targeting of activated T cells in vitro." JOURNAL OF IMMUNOLOGY, (1993 FEB 15) 150 (4) 1619-28.

D10: LONDEI M ET AL: "Cloning of activated t cells from rheumatoid arthritis joints detection of collagen type ii specific cells." SYMPOSIUM ON MOLECULAR AND CELLULAR MECHANISMS OF HUMAN HYPERSENSITIVITY AND AUTOIMMUNITY HELD AT THE 17TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 17-23, 1988. J CE

D11: COHEN S B ET AL: "High level of interleukin-10 production by the activated T cell population within the rheumatoid synovial membrane." ARTHRITIS AND RHEUMATISM, (1995 JUL) 38 (7) 946-52.

D12: EP 0 896 999 A (SHIONOGI & CO) 17 February 1999 (1999-02-17)

D13: MCINNES I B ET AL: "Interleukin 15: a proinflammatory role in rheumatoid arthritis synovitis" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 19, no. 2, 1 February 1998 (1998-02-01), pages 75-79, ISSN: 0167-5699

See in particular those passages cited as relevant in the International Search Report.

ad section III

1. Claims 1-4,6-10,13-15,23-25,49,50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. With respect to the subject-matter examiner in the present international preliminary examination, please see International Search Report Box I relating to the observations on claimed subject-matter found unsearchable.

ad section IV

The following 2 separate inventions have been identified:

Invention I (part of claims 1-4 and 6-50)
Method of treatment of a chronic inflammatory disease in a patient comprising the administration of a compound that selectively inhibits cytokine-activated T cells (designated Tck by the Applicant). Methods for identifying said compounds as well as the compounds per se.

Invention II (claims 51-55)
A preparation of T-cell enriched cells wherein the cells are from tissue from a site of inflammation in a patient suffering from a chronic inflammatory disease.

The present application does not meet the requirement of unity of invention as there exists no single general inventive concept among the two separate inventions as defined above.
According to the present description, page 4, last paragraph to page 5 first paragraph, the problem to be solved by invention I would a priori appear to be a method for identifying compounds with efficacy in the treatment of chronic inflammatory disease.

The solution to said problem consists of compounds which selectively target, either directly or indirectly via cytokine-stimulated T cells, macrophages/monocytes responsible for the production of pro-inflammatory cytokines in RA synovial tissue, for instance, compounds which inhibit cytokine-activated T cells, in particular NF-kappaB inhibitors, such as IkappaBalpha.

The concept of the usefulness of such compounds for inhibiting the above-mentioned pro-inflammatory cytokines released from macrophages in diseases like RA, is already known from the prior art document "Proceedings of the National Academy of Sciences of the United States of America: July 7th, 1998, vol.95, pages 8211-8215, see in particular abstract and the sections "results" and "discussion"). Said document highlights the relevance of NF-kappaB inhibitors in the decrease of the proinflammatory cytokine TNFalpha in rheumatoid arthritis.

The subject-matter of invention II consists of a preparation of T-cell enriched cells originating from a site of inflammation in a patient suffering from a chronic inflammatory disease. In the claims of invention II, there is no mentioning of the compounds of invention I, and it is not clear what problem the claimed T-cell enriched cells are actually supposed to solve. In this context, it should be noted that none of the claims of invention II mention cytokine-activated T-cells or compounds influencing the function of the latter.
A use of the T-cell enriched cells of invention II as "therapeutic components" which would have to selectively inhibit "cytokine activated"- T-cells (as in invention I) has no support in the application as originally filed, and it is not clear how this interaction would actually solve the problem of invention I.

Said two inventions thus do, neither a priori nor a posteriori in the light of the cited prior art, share any novel and inventive technical features which solve the problem of invention I as defined above.

ad section V

Invention I

1. The present invention relates to treatment of chronic inflammatory disease comprising the administration of an inhibitor of cytokine activated T cells (arbitrarily designated as Tck cells) opposed to TRC activated cells (e.g. by anti-CD3 antibodies). The only claimed inhibitors searched are nf-kappa inhibitors such as IkappaBalpha and antibodies having specificity for generally activated T-cells.

2. The present application does not satisfy the requirements of Article 33(2)PCT for lack of novelty of claims 26 and 47 in the light of the cited prior art (see in e.g.D1 which discloses compounds which have efficacy in the treatment of chronic inflammatory disease such as nf-kappa inhibitors, for instance IkappaBalpha).

3. The remaining claims might formally satisfy the requirements of Article 33(2) PCT but nevertheless contravene Article 33(3) PCT:

(With respect to the novelty of any claims relating to Tck-cell specific antibodies see section VIII below).

3.1 Document D1 discloses that adenoviral infection with IkappaBalpha inhibits the production of TNFalpha by macrophages in rheumatoid arthritis. Said document does not explicitly describe that patients were actually treated but strongly suggests to use the above inhibitor as a therapeutic agent in the present context.

In the light of said document, the subject-matter of claims 1-4,6,7 and 47-50 are thus considered to lack inventive step.

3.2 Document D3 discloses that cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumour necrosis factor alpha and suggests a possible relevance in the pathophysiology of RA.

In this respect, the proinflammatory role of TNF is well known, e.g. from D2 which discloses strategies to restrain TNFalpha in e.g RA with various components including NF-kappaB inhibitors, anti-TNFalpha antibodies and various cytokines, synthetic drugs.

3.2.1

Thus, in the light of D1 combined with D2 and D3, methods for identifying compounds with a desired RA-treatment efficacy, in this case by testing the ability to selectively inhibit Tck cells would appear to be straightforward.
Consequently the subject-matter of claim 8 lacks an inventive step. Claims 9-25 related to said claim 8 concern embodiments which are either known per se or do not appear to contain any additional features which would confer the required inventive step to the said claimed subject-matter. With respect to the subject-matter of claims 23-25 which relate to a method for detecting PI3 kinase activation activity, please see section VIII below).

3.2.2

The same objection applies to the antibodies, methods for making the same, cells expressing the same, methods for identifying the same as well as components containing the same according to claims 27-41 or to the related subject-matter as defined in claims 42 to 46. With respect to antibodies against "activated" T-cells,

see e.g. D6 which discloses antibodies against "activated" T cells and induction of microglial production of TNF alpha production by the activated T-cells. This document mentions the relevance of its findings in various areas, e.g. inflammatory diseases such as RA. Thus, even if the major objections under Articles 5 and 6 PCT listed in section VIII could be overcome, said embodiments would still lack inventive step in the light of said document, in combination with any of the documents as cited above.

Invention II

All of claims 51 to 55 lack novelty in view of documents D10 to D12.
All of the latter disclose T-cell preparations originating from a site of inflammation (e.g. synovium) in a patient suffering from RA.

ad section VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents cited in sections IV and V above is not mentioned in the description, nor are these documents identified therein.

2. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

   If the Applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

ad section VIII

1. As already mentioned in the Search Report, present claims 1-3, 6 and 26-50 relate to an extremely large number of possible compounds and the use thereof

(see e.g. all the known compounds cited at pages 19 and 20 of the present description as well as the numerous further possibilities cited throughout the application). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure for a part of said claims.

2. In this context it should be noted that the present description and examples do not give any precise examples of PI3 kinase "activators", but merely mentions "inhibitors" of said enzyme in the context of detection methods for identifying compounds which would have efficacy in the treatment of a chronic inflammatory disease. Said claim 5 which was not searched as the number of possibilities covered by the scope of said claim is unduly broad not allowing a meaningful search to be performed. The same objection is valid for claims 23-25 which relate to the subject-matter of claim 5 and can therefore not be examined.

   The same remark is valid mutatis mutandis for the antibodies throughout claims 26-50 (including the claimed nucleic acids encoding antibody/cytotoxin conjugates and claimed vectors and host cell lines related thereto) as the present description or examples do not disclose any "specific antibodies" which have actually been produced (no hybridomas). The examples merely recite a possible protocol with respect to a production of such antibodies, without however actually describing "produced" or "isolated" antibodies which would have the required specificity for "cytokine activated" T-cells. The required support withing the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT are thus not given. It is for instance also not sure which cytokines, or combination of the same, would have to be used to activate T-cells which would show adequate antigenic determinants identifiable by specific antibodies.
   Thus it should be noted that only antibodies which are specific for "activated T-cells" (irrespective of their mode of activation) in general have been searched in the given context (in this respect see prior art documents D.....).

3. The term Tck cells used throughout the claims is considered to be an arbitrary designation and not clearly defined feature in the sense of Article 6 PCT.

4. The term "antibody-**like**" molecule is considered to be vague and indefinite (Article 6 PCT).

European Patent Office
P B 5818
Patentlaan 2
2280 HV Rijswijk (ZH)
THE NETHERLANDS

11 January 2002

Sent by fax

Dear Sirs

International Patent Application No. PCT/GB00/03660
THE MATHILDA AND TERENCE KENNEDY INSTITUTE OF RHEUMATOLOGY
Our ref: ICOW/P23194PC

This is a response to the written communication under Rule 66 PCT of 9 October 2001. We are grateful for the exceptional two day extension to the deadline for filing a response, as agreed during the telephone conversation of 7 January 2002 between our Dr Stephen Smith and the IPEA Formalities Officer.

We enclose amended pages 80 to 88 to replace the corresponding pages currently on file.

Claim amendments

Claims 1, 27, 30 and 33 (renumbered as Claims 1, 25, 28 and 31) are amended such that the term T_{ck} cells is defined. Basis for this amendment can be found at page 5, line 16 of the description.

Claim 1 is further amended such that it is limited by the feature of a compound which selectively inhibits T_{ck} cells by rendering the T_{ck} cells functionally inhibited with respect to their ability to activate monocytes and/or by reducing the number of the T_{ck} cells, *i.e.* which inhibits T_{ck} cells *directly*. Basis for this amendment can be found at page 5, lines 23 to 25 of the description.

cont/....

Old Claims 4 and 5 are deleted and replaced with New Claims 4 and 5. New Claim 4 is directed to a preferred embodiment of the method of Claim 1 wherein the compound is an antibody-like molecule. New Claim 5, which is dependent on Claim 4, is directed to preferred antibody-like molecules.

Claim 7 is deleted.

Claim 8 (renumbered as Claim 7) is limited by the feature of the method being conducted *in vitro*. Implicit basis for this amendment can be found at page 11, lines 10 to 14 of the description.

Claims 9 and 10 are renumbered as Claims 8 and 9.

Claims 11 is deleted.

Claim 12 (renumbered as Claims 10) is amended such that it is limited to the feature of T_{ck} cells.

Claims 13 to 25 are renumbered as Claims 11 to 23.

Claim 26 (renumbered as Claim 24) is amended such that it is limited to compounds identified by the methods of the invention.

Claims 27 to 50 are renumbered as Claims 25 to 48.

Claims 51 to 55 are deleted.

Comments

The following sections correspond to the numbered sections of the written opinion:

Section III

The Examiner asserts that Claims 1 to 4, 6 to 10, 13 to 15, 23 to 25, 49 and 50 relate to subject matter covered by the provisions of Rule 67.1(iv) PCT, *i.e.* methods of treatment of the human or animal body.

cont/....

Claim 8 (renumbered Claim 7) is amended such that it is limited to *in vitro* screening methods. Hence, we submit that the Examiner's objection is obviated in relation to Claims 8 to 10, 13 to 15 and 23 to 25.

In relation to Claim 50 (renumbered Claim 48), we submit that the Examiner's objection is ill-founded since this claim is dependent on second medical use Claim 48 (renumbered Claim 46), to which the Examiner has not objected.

Section IV

The Examiner has maintained the lack of unity objection raised during the preparation of the international search report.

In order to expedite prosecution of this application, Claims 51 to 55 are deleted.

Section V

(i) Claims 26 and 47: Alleged lack of novelty over D1

The Examiner asserts that Claims 26 and 47 lack novelty over D1.

Claim 26 (renumbered as Claim 24) is amended such that it is limited to compounds *identified* by the screening methods of the present invention. Neither D1 nor any of the other prior art documents cited by the Examiner disclose or suggest a compound identified by such methods.

Claim 47 (renumbered as Claim 45) is dependent on Claim 26 (renumbered Claim 24).

Hence, we submit that the subject matter of Claims 26 and 47 (renumbered Claims 24 and 45) is novel.

cont/....

(ii) Claims 1 to 4, 6, 7 and 47 to 50: Alleged lack of inventive step in view of D1

The Examiner asserts that Claims 1 to 4, 6, 7 and 47 to 50 lack an inventive step in view of D1.

Claim 1 is amended such that it is limited by the feature of a compound which selectively inhibits T_{ck} cells by rendering the cells functionally inhibited and/or by reducing the number of the cells, *i.e.* which inhibits T_{ck} cells *directly*.

In contrast, the adenoviral IκBα infection system disclosed in D1 comprises "*the successful delivery of genes to ... normal human macrophages*" (see D1, abstract, emphasis added). D1 neither discloses nor suggests a method of treatment of a chronic inflammatory disease comprising administering a compound which has a *direct* inhibitory action on T_{ck} cells.

Hence, we submit that the subject matter of Claims 1 to 4, 6 and 7 (renumbered Claims 1 to 6) is not rendered obvious by D1.

In view of the amendment of Claim 26 (renumbered Claim 24), we also submit that the subject matter of Claims 47 to 50 (renumbered Claims 45 to 48) is inventive over D1.

(iii) Claims 8 to 25: Alleged lack of inventive step in view of D1 combined with D2 and D3

The Examiner asserts that Claims 8 to 25 are rendered obvious by the disclosures of D1 when considered in combination with D2 and D3.

D2 discloses agents for suppressing the formation or activity of TNFα. No mention is made of the role of cytokine-activated T cells in the formation or activity of TNFα.

D3 discloses the regulatory role of cytokine-stimulated T cells on TNFα production in monocytes.

cont/....

The EPO Boards of Appeal have approved as a test for inventive step the question "was the claimed invention obvious to try with a reasonable expectation of success?". Thus, the test is two-pronged. Was the invention "obvious to try"? Was there a "reasonable expectation of success"? Only if the person skilled in the art would have found the claimed invention obvious to try and would have reasonably expected to succeed can a conclusion of obviousness be reaches.

In raising an obviousness objection based on D1 in combination with D2 and D3 it would appear that, in the present case, the Examiner has fallen into the trap of assessing obviousness with the benefit of hindsight, which is impermissible.

As stated above, neither D1 nor D2 disclose or suggest a role of cytokine-activated T cells in the production of TNFα by monocytes. Although D3 comments that such T cells might contribute to the overproduction of TNFα in rheumatoid arthritis (RA), this is purely speculative:

"*The results ... suggest that cytokine-stimulated T cells ... may contribute to the continuous excessive production of TNFα in the RA joint*"

(D3, abstract, emphasis added)

However, D3 provides no evidence whatsoever in support of this hypothesis. In particular, D3 provides no evidence that compounds which inhibit cytokine-stimulated T cells would have potential utility in the treatment of chronic inflammatory diseases such as RA.

Indeed, the Examiner acknowledges that D3 merely "*suggests a possible relevance*" of cytokine-activated T cells in the pathophysiology of RA (see item 3.2 of the written opinion, emphasis added).

Hence, on reading D3 (optionally in combination with D1 and D2), a person skilled in the art would, at best, merely have a hope to succeed in providing the methods of the present invention. Such a hope to succeed falls far short of the reasonable expectation of success required for a conclusion of obviousness to be reached.

cont/....

Indeed, it would be counter-intuitive to try to identify compounds with efficacy in the treatment of RA by screening for a selective inhibitory effect on cytokine-stimulated T cells since it was known in the art that both cytokine-stimulated T cells and T cell receptor-stimulated T cells induced TNFα production in monocytes (for example, see D3 abstract). Hence, a skilled person would expect that non-selective inhibition of T cells would be more likely to be therapeutically beneficial in the treatment of chronic inflammatory diseases.

Hence, we submit that the subject matter of Claims 8 to 25 (renumbered Claims 7 to 23) is not rendered obvious by the disclosures of D1 when considered in combination with D2 and D3.

(vi) Claims 27 to 41: Alleged lack of inventive step in view of D1 combined with D2 and D3

The Examiner also asserts that Claims 27 to 46 are rendered obvious in view of the disclosures of D1 when considered in combination with D2 and D3.

However, as stated above, D3 merely speculates that cytokine-stimulated T cells might be involved in the pathophysiology of RA.

Hence, a skilled person could not and would not reasonably have expected that antibodies with specificity for cytokine-stimulated T cells would have utility in the treatment of chronic inflammatory diseases. Hence, a skilled person would have no motivation to make such antibodies.

We therefore submit that the subject matter of Claims 27 to 46 (renumbered Claims 25 to 46) is not rendered obvious by the disclosures of D1 when considered in combination with D2 and D3.

Section VII

We note the Examiner's comments regarding the identification of prior art documents D1, D2 and D3 in the description.

cont/....

We will attend to this objection during the regional/national phase of this application.

Contrary to the Examiner's assertion, D3 is identified at page 4, lines 1 to 6 of the description as filed.

Section VIII

(i) Claims 1 to 3, 6 and 26 to 50: Alleged lack of support and sufficiency

The Examiner has raised an objection to the subject matter of Claims 1 to 3, 6 and 26 to 50 on the grounds that they do not meet the requirements of Art 5 and 6 PCT.

As discussed above, the claims are amended to define more closely the subject matter of the invention. Specifically, Claim 1 is amended such that it is limited by the feature of a compound which has a direct inhibitory effect on T_{ck} cells. Examples of such compounds include antibody-like molecules with specificity for T_{ck} cells. Methods comprising the administration of antibody-like molecules are explicitly claims in new Claims 4 and 5.

The description contains an extensive disclosure of methods of producing antibodies and antibody-like molecules with specificity for T_{ck} cells (see page 21, line 13 to page 45, line 14).

Hence, we submit that the subject matter of Claims 1 to 3, 6 and 26 to 50 (renumbered Claims 1 to 3, 6 and 24 to 48) is fully supported by the description.

We refer the Examiner to the following passage from the *PCT Examination Guidelines*:

> *"As a general rule, a claim should be regarded as supported by the description unless, exceptionally, there are well-founded reasons for believing that the skilled man would be unable, on the basis of the information given in the application as filed, to extend the particular teaching of the description to the whole of the field claimed by using*

cont/....

routine methods of experimentation or analysis ... The examiner should raise an objection of lack of support only if he has well-founded reasons. Where objection is raised, the reasons should, where possible, be supported specifically by a published document".

PCT Examination Guidelines III-6.3 (emphasis added)

In the absence of such 'well-founded reasons' and a supporting document being identified by the Examiner, we submit that the objection should be withdrawn.

Likewise, in relation to the objection under Art 5 PCT (sufficiency of disclosure), we refer the Examiner to Decision T 19/90 of the EPO Technical Boards of Appeal, wherein it states that:

"*Only if there are serious doubts, substantiated by verifiable facts, may an application be objected to for lack of sufficient disclosure*".

Decision T 19/90, paragraph 3.3 (emphasis added)

In the present case, the Examiner conspicuously fails to provide any verifiable facts to support the objection on the grounds of a lack of sufficiency. In the absence of such verifiable facts, we submit that the Examiner's objection should be withdrawn.

We appreciate that the Examiner is acting for the EPO as IPEA and that case-law of the EPO Boards of Appeal is not, strictly speaking, appropriate. However, the same considerations are to be taken into account under Article 5 PCT as under Article 83 EPC, so in the present case the cited EPO case-law should be persuasive.

(ii) Alleged lack of clarity

The Examiner has raised an objection to the terms 'T_{ck} cells' and 'antibody-like molecule' on the grounds of a lack of clarity.

cont/....

The claims are amended so as to define the term 'T_{ck} cells'. In addition, the term 'T_{ck} cells' is further defined at page 5, lines 16 to 19 of the description.

In relation to the term 'antibody-like molecule', we submit that this term is a well-known term of art which would be clearly understood by a person skilled in the art. The term 'antibody-like molecule' is also defined in the description at page 21, line 26 to page 22, line 3 and at page 23, lines 10 to 19.

In light of the above claim amendments and comments, we request reconsideration of the objections detailed in the written opinion.

Any amendment is not to be construed as abandonment of subject matter.

Yours sincerely

John S Miles PhD ses/jp

Enc: Amended pages 80 to 88

CLAIMS

1. A method of treatment of a chronic inflammatory disease in a patient, the method comprising the administration to the patient of a compound that selectively inhibits T_{ck} cells.

2. A method according to claim 1 wherein said compound selectively inhibits T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes.

3. A method according to claim 2 wherein the cytokine is tumour necrosis factor-α.

4. A method according to any one of claims 1 to 3 wherein said compound selectively inhibits NF-κB.

5. A method according to any one of claims 1 to 3 wherein said compound selectively activates PI3 kinase.

6. A method according to any one of claims 1 to 5 wherein said compound is a nucleic acid molecule encoding a polypeptide which selectively inhibits T_{ck} cells.

7. A method according to claims 6 wherein the nucleic acid molecule encodes an NF-κB inhibitor, preferably IκBα.

8. A method of identifying a compound with efficacy in the treatment of a chronic inflammatory disease comprising the step of testing the compound for an ability to selectively inhibit T_{ck} cells.

9. A method according to Claim 8 wherein testing the compound for an ability to selectively inhibit T_{ck} cells comprises testing the compound for an ability to selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes.

10. A method according to claim 9 wherein the cytokine is tumour necrosis factor-α.

11. A method according to claim 10 wherein said method comprises the following steps:

(i) pre-incubating monocytes with a compound to be tested;

(ii) resuspending said pre-incubated monocytes in the absence of the test compound;

(iii) stimulating said resuspended monocytes by co-culturing with either T_{ck} cells or T_{tcr} cells; and

(iv) assaying for TNFα production by said stimulated monocytes.

12. A method according to claim 10 wherein said method comprises the following steps:

(i) pre-incubating separate cultures of T_{ck} cells and T_{tcr} cells with a compound to be tested either prior to fixation or during their activation in culture;

(ii) resuspending said T_{ck} cells and T_{tcr} cells in the absence of the test compound;

(iii) stimulating monocytes by co-culturing with said resuspended T_{ck} cells or T_{tcr} cells; and

(iv) assaying for TNFα production by said stimulated monocytes.

13. A method according to any one of claims 8 to 12 wherein the chronic inflammatory disease is a disease of humans.

14. A method according to any one of claims 8 to 13 wherein the chronic inflammatory disease is rheumatoid arthritis.

15. A method according to any one of claims 8 to 14 wherein testing the compound for an ability to selectively inhibit T_{ck} cells or selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits NF-κB inhibition.

16. A method according to claim 15 wherein NF-κB inhibition is constituted by a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF-κB promoter DNA oligonucleotide.

17. A method according to claim 16 wherein a reduction in the binding of nuclear extracts, derived from monocytes exposed to the compound, to an NF-κB promoter DNA oligonucleotide is determined by an electrophoretic mobility shift assay (EMSA).

18. A method according to any one of claims 15 to 17 wherein NF-κB inhibition is deemed to exist if the binding of NF-κB to an NF-κB promoter DNA oligonucleotide is reduced to no more than 50%, preferably no more than 20%, 10%, 5% or 1%, and most preferably is substantially zero.

19. A method according to claim 15 wherein NF-κB inhibition is constituted by a reduction in expression of the NF-κB gene.

20. A method according to claim 19 wherein a reduction in the expression of the NF-κB gene is determined by a reporter gene assay.

21. A method according to claim 20 wherein the reporter gene assay comprises coupling a β-galactosidase gene to the NF-κB gene and determining a reduction in β-galactosidase activity.

22. A method according to claim 21 wherein β-galactosidase activity is reduced to no more than 50%, preferably no more than 20%, 10%, 5% or 1%, and most preferably is substantially zero.

23. A method according to any one of claims 8 to 14 wherein testing the compound for an ability to selectively target T_{ck} cells or selectively inhibit T_{ck} cell-induced release of one or more pro-inflammatory cytokines from monocytes comprises determining whether the compound exhibits PI3 kinase activation.

24. A method according to claim 23 wherein PI3 kinase activation is constituted by an increase in PI3 kinase activity in monocytes exposed by the compound.

25. A method according to claim 24 wherein PI3 kinase activation is deemed to exist if there is an increase in PI3 kinase activity equivalent to at least 50% of the increase induced by IL-10 stimulation (100 ng/ml for 2 minutes), preferably at least 70%, 80% or 90%, and most preferably greater than the increase induced by IL-10 stimulation.

26. A compound identifiable or identified as having efficacy in the treatment of a chronic inflammatory disease by a method according to any one of claims 8 to 24.

27. An antibody-like molecule having specificity for T_{ck} cells.

28. An antibody-like molecule according to Claim 27 selected from the group of molecules consisting of Fab molecules, $F(ab')_2$ molecules, Fv molecules, disulphide-linked Fv molecules, single chain Fv (scFv) molecules and single domain antibodies (dAbs).

29. An antibody-like molecule according to Claim 27 or 28 wherein said antibody-like molecule is humanised.

30. A method of making an antibody-like molecule according to any one of Claims 27 to 29 comprising immunising an animal with a population of T_{ck} cells.

31. An isolated cell that expresses an antibody-like molecule according to any one of claims 27 to 29.

32. An isolated cell according to claim 31 wherein the cell is a hybridoma cell.

33. A method for identifying an antibody-like molecule according to any one of Claims 27 to 29 comprising the following steps:

(i) providing a population of T_{ck} cells; and

(ii) using said T_{ck} cells to screen a library of antibody-like molecules.

34. A method according to Claim 33 wherein the antibody-like molecule library is a phage display library.

35. A compound comprising a target cell specific portion and a directly or indirectly cytotoxic portion, wherein the target cell specific portion comprises an antibody-like molecule according to any one of Claims 27 to 29.

36. A compound according to Claim 35 wherein the cytotoxic portion is a directly cytotoxic portion selected form the group consisting of radionuclides, ricin, ribonuclease, deoxyribonuclease, and *Pseudomonas* exotoxin A

37. A compound according to Claim 35 wherein the cytotoxic portion is indirectly cytotoxic.

38. A compound according to Claim 35 wherein the cytotoxic portion is capable of inducing apoptosis of the target cells.

39. A compound according to Claim 35 or 38 wherein the cytotoxic portion is an enzyme.

40. A compound according to any one of Claims 35 to 39 wherein the target cell specific portion and the cytotoxic portion are fused.

41. A compound according to Claim 40 wherein the target cell specific portion and the cytotoxic portion are separated by a linker sequence.

42. A nucleic acid molecule encoding a compound according to Claim 35 or 41.

43. A vector comprising a nucleic acid molecule according to Claim 42.

44. A host cell line comprising a vector according to Claim 43.

45. A pharmaceutical formulation comprising a antibody-like molecule according to any one of Claims 27 to 29 or a compound according to any one of Claims 26 or 35 to 41 and a pharmaceutically acceptable carrier.

46. An antibody-like molecule according to any one of Claims 27 to 29 or a compound according to any one of Claims 35 to 41 for use in medicine.

47. A compound according to Claim 26 for use in the treatment of a chronic inflammatory disease.

48. Use of an antibody-like molecule according to any one of Claim 27 to 29 or a compound according to any one of Claims 26 or 35 to 41 in the preparation of a medicament for the treatment of a chronic inflammatory disease.

49. A method of treating a patient with a chronic inflammatory disease comprising administering to said patient a therapeutically effective amount of an antibody-like molecule according to any one of Claim 27 to 29 or a compound according to any one of Claims 26 or 35 to 41.

50. The use according to Claim 48 wherein the chronic inflammatory disease is rheumatoid arthritis.

51. A preparation of T-cell enriched cells wherein the cells are from tissue from a site of inflammation in a patient suffering from a chronic inflammatory disease.

52. A preparation of cells according to Claim 51 wherein the chronic inflammatory disease is rheumatoid arthritis.

53. A preparation of cells according to Claim 51 or 52 wherein the tissue is from the synovium.

54. A preparation of cells according to any one of Claims 51 to 53 wherein the T-cell enriched cells are CD3+-enriched cells.

55. A preparation of cells according to any one of Claims 51 to 53 wherein the T-cell enriched cells are non-adherent cells.